

HEART FAILURE WITH PRESERVED AND MILDLY REDUCED EJECTION FRACTION IN ELDERLY

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Abstract. Heart failure (HF) is an important public health problem, with an increased prevalence both in the general population, but especially in people over 65 years, with high morbidity and mortality, with high hospitalization rate, with significant impact on functional capacity and quality of lives of patients, whose management involves high costs. The 2016 and 2021 ESC guidelines for heart failure introduced a third category of heart failure for ejection fraction of 41-49%, defined as heart failure with mildly reduced ejection fraction. The prevalence of heart failure with mildly reduced ejection fraction in the total population of patients with HF is 10-25%. This appears to be an intermediate clinical entity between heart failure with reduced ejection fraction and preserved in some aspects, but more similar to that with low ejection fraction in others, especially with respect to the high prevalence of ischemic heart disease in these patients. Heart failure with preserved ejection fraction is the most common form in the elderly. Heart failure with preserved and mildly reduced ejection fraction in the elderly is a challenge for the clinician, both in terms of diagnosis, prognosis and treatment. The clinical picture of heart failure is often atypical and may be masked by the presence of comorbidities. There are currently no evidence-based treatment guidelines for elderly patients, which makes managing heart failure an even greater challenge.

Key words: heart failure, ejection fraction, elderly

Rezumat. Insuficiența cardiacă (IC) reprezintă o problemă importantă de sănătate publică, având o prevalență crescută atât în populația generală, dar mai ales la persoanele peste 65 de ani, cu morbiditate și mortalitate ridicate, cu rată crescută de spitalizare, cu impact important asupra capacității funcționale și a calității vieții pacienților, a cărui management implică costuri ridicate. Ghidurile ESC din 2016 și 2021 pentru insuficiență cardiacă au introdus o a treia categorie de insuficiență cardiacă pentru fracția de ejeecție de 41-49%, definită ca insuficiență cardiacă cu fracție de ejeecție ușor scăzută. Prevalența insuficienței cardiace cu fracție de ejeecție ușor redusă în populația totală a pacienților cu IC este de 10-25%. Aceasta pare a fi o entitate clinică intermediară, în unele privințe, între insuficiența cardiacă cu fracție de ejeecție redusă și păstrată, dar mai asemănătoare cu cea cu fracție de ejeecție scăzută în altele, în special în ceea ce privește prevalența ridicată a bolii cardiace ischemice la acești pacienți. Insuficiența cardiacă cu fracție de ejeecție păstrată este cea mai frecventă formă la vârstnic. Insuficiența cardiacă cu fracție de ejeecție păstrată și ușor redusă la vârstnic reprezintă o provocare pentru clinician, atât din punct de vedere al diagnosticului, al prognosticului, cât și al tratamentului. Tabloul clinic al insuficienței cardiace este adesea atipic și poate fi mascat de prezența comorbidităților. În acest moment nu există ghiduri de tratament bazate pe dovezi pentru pacienții vârstnici, ceea ce face ca managementul insuficienței cardiace să fie o provocare și mai mare.

Cuvinte cheie: insuficiență cardiacă, fracție de ejeecție, vârstnici

INTRODUCTION

A clinical condition known as heart failure (HF) is caused by structural and /or functional heart defects, which lead to a decrease in cardiac output and /or higher intracardiac filling pressures at rest or exertion. With high prevalence and incidence rates, high morbidity and mortality, low functional capacity and quality of life, especially among the elderly, as well as substantial economic

costs, HF is a significant public health problem. However, the incidence of HF has stabilized and appears to be declining in industrialized countries, but the prevalence is increasing due to aging population, ischemic heart disease that is better treated and patients live longer due to the availability of effective therapies that prolong life in patients with HF and after acute myocardial infarction [1, 2]. The prevalence of heart failure in adults is 1-2% and increases with age, reaching >10%

in people over 70 years. It is estimated that approximately 60% of patients with heart failure have a low ejection fraction, 24% have a mildly reduced ejection fraction and 16% have a preserved ejection fraction [3]. The left ventricular ejection fraction (FE), generally measured by echocardiography, remains the cornerstone of diagnosis, characterization, prognosis, patient triage, and IC treatment selection.

HF with low EF (HFrEF, defined as EF <40%) is well characterized and effective therapies are available for patients with HFrEF. In 2016, the European Society of Cardiology (ESC) introduced a new classification of heart failure, which was maintained in the guide in 2021, in three categories, depending on the value of the left ventricular ejection fraction. Thus, the current classification of heart failure includes HF with preserved ejection fraction (HFpEF characterized by EF >50%), HF with mildly reduced ejection fraction (HFmrEF, FE 41-49%) and with reduced ejection fraction (FE <40%) [3].

HEART CHANGES IN THE ELDERLY

The hallmark of cardiac aging is a decrease in the diastolic function of the left ventricle. Age-related diastolic dysfunction is responsible for the high prevalence of HFpEF, a disease that was previously called diastolic heart failure. Patients with HFpEF usually present with diastolic abnormalities, including delayed early relaxation, stiffening of the myocardium and myocytes, and changes associated with the dynamics of ventricular filling [4].

The systolic function of the left ventricle is affected by the aging process by reducing the cardiac reserve during exertion, decreasing myocyte contractile function and decreasing the maximum frequency of the ventricular heart rate that an elderly person can reach in case of physical exertion. However, the ejection fraction of the left ventricle is not affected by the aging process [4].

Regarding the cardiac excitoconducting system, the aging process is associated with a significant decrease in the number of pacing cells at the sinoatrial node. This causes an increase in the incidence of sinoatrial node dysfunction in the elderly, manifested by palpitations, dizziness, presyncopal status or syncope, fatigue and even confusing syndromes [4].

At the structural level, the most important phenomenon observed with age is the increase in the thickness of the left ventricular wall due to the increase in the size of cardiomyocytes. This phenomenon is often associated with dilation or hypertrophy of the left atrium, caused by increased intraventricular pressure. Structural changes are due to cellular changes. The most important cellular changes are the decrease in the number of myocytes and excitoconducting cells, responsible for the occurrence of ventricular hypertrophy and myocardial fibrosis, and amyloid deposition [5].

CLINICAL DIAGNOSIS

The most common etiologies of heart failure with preserved or mildly reduced ejection fraction in the elderly are hypertension and acute and chronic coronary heart disease. Other common etiologies are age-related diastolic dysfunction, valvopathies, pericardial pathology and non-ischemic heart disease caused by alcohol consumption, post-chemotherapy or inflammatory myocarditis. Triggers or aggravating factors of heart failure are chronic iron deficiency anemia or thiamine deficiency, hyperthyroidism, fever, some drugs, high-salt diet, endocrine diseases, chronic obstructive pulmonary disease, nonadherence to treatment, arrhythmias, renal failure, and pulmonary embolism [6]. The diagnosis of heart failure requires the presence of specific signs and/or symptoms, summarized in Tab. I, according to the ESC guideline and the objectification of heart dysfunction [3].

Tab. I Signs and symptoms of heart failure according to 2021 ESC Guideline

Symptoms	Signs
<i>Typical</i>	<i>More specific</i>
Breathlessness	Elevated jugular venous pressure

Orthopnea Paroxysmal nocturnal dyspnea Reduced exercise tolerance Fatigue, tiredness, increased time to recover after exercise Ankle swelling	Hepatojugular reflux Third heart sound (gallop rhythm) Laterally displaced apical impulse
<i>Less typical</i>	<i>Less specific</i>
Nocturnal cough Wheezing Bloated feeling Loss of appetite Confusion (especially in the elderly) Depression Palpitation Dizziness Syncope	Weight gain (>2 kg/week) Weight loss (in advanced HF) Tissue wasting (cachexia) Cardiac murmur Peripheral oedema (ankle, sacral, scrotal) Pulmonary crepitations Pleural effusion Tachycardia Irregular pulse Tachypnoea Cheyne-Stokes respiration Hepatomegaly Ascites Cold extremities Oliguria Narrow pulse pressure

Signs and symptoms of HF have low sensitivity and specificity in clinical diagnosis in elderly patients. Typical signs and symptoms are known to be less common in the elderly population due to the presence of other comorbidities, along with atypical manifestations such as confusion, drowsiness, anorexia and low activity, especially in patients with dementia. Dyspnea is the primary symptom of HF, the clinical expression of elevated lung pressure that can be underestimated in sedentary elderly patients and can be caused by other factors, such as chronic lung disease or anemia. On the other hand, fatigue, which is also a predominant symptom, may be related to hypoperfusion of skeletal muscle. Thus, if the patient complains of fatigue, this should not be considered a common symptom. Fine audible crackles at the base of the lungs may be common in the elderly due to prolonged bed rest and physical inactivity, and leg edema may be due to chronic venous insufficiency or malnutrition [1, 7].

PARACLINICAL DIAGNOSIS

The diagnostic suspicion of heart failure arises in the presence of specific signs and symptoms and is confirmed based on elevated serum BNP values and echocardiography.

Natriuretic peptide levels increase with age and may vary in the presence of comorbidities such as obesity, renal failure or atrial fibrillation. Accordingly, they should be interpreted in conjunction with clinical and echocardiographic findings. B-type natriuretic peptide (BNP) is an important marker for the prediction and prognosis of heart failure, its main secretion being from the left ventricle. The benefit of determining its plasma level in patients with dyspnea is well known, helping to differentiate the diagnosis between respiratory pathologies (COPD) and heart failure.[8] Serum BNP levels >100ng/L or NT-proBNP >300pg/L, associated with echocardiographic abnormalities support the diagnosis of heart failure [7].

Echocardiography (Tab. II) is crucial for identifying the type of HF (HFpEF, HFmrEF, HFfrEF), cardiac structural damage (left ventricular hypertrophy and dilation of the left atrium), diastolic dysfunction, dilation of the vena cava and pulmonary hypertension and may help clarify the etiology of the disease (parietal kinetics abnormalities as an indirect sign of ischemic heart disease). Echocardiography is also important in diagnosis of treatable causes of heart failure, such as aortic stenosis or mitral valve regurgitation [7].

Tab. II Specifics of echocardiography in elderly heart failure patients

Most frequent echocardiographic abnormalities in elderly subjects with HF	Characteristics/main causes
Preserved LVEF	LVEF \geq 50% Variables in favor of the diagnosis: LV hypertrophy; LA dilation; diastolic dysfunction
Diastolic dysfunction	At least three of the following criteria (if LVEF \geq 50%): average E/e' $>$ 14; septal e' velocity $<$ 7 cm/s or lateral e' velocity $<$ 10 cm/s; tricuspid regurgitation velocity $>$ 2.8 m/s; LA volume index \geq 34 mL/m ²
LV hypertrophy	LV mass $>$ 95 g/m ² (women), $>$ 115 g/m ² (men) Main causes: hypertension; aortic stenosis; cardiac amyloidosis
Mildly reduced LVEF	LVEF 41-49% Commonly in men, younger, and more likely to have coronary artery disease (CAD) Associated features: LV hypertrophy, LA dilatation, wall motion abnormalities
Reduced LVEF	LVEF $<$ 40% Less frequent in elderly versus younger subjects with HF Associated features: LV dilation; wall motion abnormalities
LA dilation	LA volume index \geq 34 mL/m ² , LA diameter \geq 40 mm Main causes: systolic or diastolic dysfunction; hypertension; valve diseases
Valve diseases	Aortic stenosis: most frequent valve disease in elderly patients with HF Severe aortic stenosis: area \leq 1 cm ² (or \leq 0.6 cm ² /m ²); aortic mean gradient \geq 40 mmHg
Pulmonary hypertension	Systolic pulmonary artery pressure $>$ 40 mmHg Main causes: heart disease; respiratory disease
Pericardial effusion	Main causes: bleeding (anticoagulant, cardiac surgery, and cardiac device); inflammation/infection; cancer; cardiac amyloidosis

The diagnosis of HFpEF requires the presence of signs and symptoms of heart failure, left ventricular ejection fraction $>$ 50% and evidence of increased filling pressure on the left side at rest or stress. Evaluation of biomarkers (increased serum levels of natriuretic peptides), cardiac structure (left atrium dilation, increased LV mass) and diastolic function (increased E/e' ratio at rest or during exertion and/or increased pressure in resting lung capillaries or with effort) are essential for the diagnosis of certainty [9].

The echocardiographic presence of concentric LV hypertrophy defined as an indexed LV mass $>$ 149 g/m² in men and 122 g/m² in women and a relative wall thickness $>$ 0.42 mm is associated with diastolic dysfunction. The volume of the left atrium indexed to the body surface area $>$ 34ml/m² is one of the major morphological criteria for the diagnosis of HFpEF. It is also important to recognize that diastolic dysfunction is not the same with increased filling pressures. In general, if the mean e' is less than 9 cm/s and the E/e' ratio is greater than 13, the diagnosis

of HFpEF is favored in the context of the structural anomalies mentioned above. Other parameters that support the diagnosis are E/A $>$ 2, deceleration time $<$ 160ms, isovolumic relaxation time $<$ 60s and estimated systolic pulmonary arterial pressure $>$ 35mmHg. Importantly, if the suspicion of HFpEF is high and the resting echocardiogram is normal, exercise Doppler echocardiogram should be considered [10].

ADDITIONAL INVESTIGATIONS

In elderly patients, once the HF has been diagnosed, a multidimensional geriatric assessment should be performed to identify comorbidities and their risks for decompensation and functional consequences, to allow appropriate adjustment of treatments. A blood panel is made to identify the precipitating factors. A complete blood count (for anemia), a basal metabolic panel (for hyponatremia, indicating a poor prognosis, and hypokalemia or proarrhythmic hyperkalemia, which are responsible for conduction disorders) and

measurement of creatinine (for renal function; estimated glomerular filtration rate by Cockcroft-Gault formula) are essential. Hepatic impairment may be present (acute cytolysis indicates hypoxic liver in case of decreased cardiac output) [7].

An electrocardiogram provides information about the etiology of heart failure (atrial fibrillation, ischemia and myocardial hypertrophy), and regular electrocardiograms are needed to follow the patient.

A chest x-ray is not necessary for the diagnosis of HF, but is useful for the diagnosis of acute pulmonary edema, the presence of pleural effusion, or damage to the lung parenchyma.

COMORBIDITIES

The comorbidities associated with elderly patients with heart failure are multiple, including atrial fibrillation, ischemic heart disease, hypertension, stroke, chronic obstructive pulmonary disease (COPD), asthma, chronic respiratory failure, diabetes, obesity, malnutrition, dementia, depression, renal failure.

Also, fragility syndrome, defined by decreased functional reserves, which increases the risk of death, hospitalization, falls and disability, has a negative impact on elderly patients by decreasing physical reserves and resistance to stressors. The link between fragility and heart failure is a complex one; the two can lead to a mutual aggravation. Some studies show that fragility is an independent risk factor in patients with heart failure. Psychiatric pathology in association with fragility syndrome and heart failure should be considered when it comes to therapeutic conduct and care of elderly patients to ensure a good quality of life [11].

NON-PHARMACOLOGICAL TREATMENT OF HEART FAILURE

Non-pharmacological treatment of HF includes an adequate sodium-restricted diet, modest alcohol consumption (less than two units of alcohol per day for men and one unit of alcohol per day for women), and smoking cessation [3]. It should be noted that in the elderly over 80 years the diet

without sodium (<3 g/day) should be avoided due to age-related renal sodium reabsorption defects, which increase the risk of hyponatremia. Additionally, people who have experienced malnutrition are more likely to develop anorexia on a sodium-free diet. Therefore, sodium consumption must be adjusted (3-6 g/day), while also maintaining an adequate calorie intake, preserving the balance of other dietary recommendations, and incorporating it into a wider treatment strategy [6].

Physical activity is highly encouraged. Cardiac rehabilitation programs provide a unique tool to achieve good physical condition after the diagnosis of HF, but also to prevent the onset of HF. Rehabilitation programs are thus a multidimensional therapy with major benefits proven by avoiding hospitalizations due to HF and improving the quality of life, significantly in the elderly [1].

PHARMACOLOGICAL TREATMENT OF HEART FAILURE WITH PRESERVED EJECTION FRACTION

Although improvements have been noted for some particular phenotypes of individuals under the overall heading of HFpEF, no medication has been demonstrated to clearly reduce mortality and morbidity in patients with HFpEF to date. Treatment should focus on easing congestion symptoms using diuretics, in the absence of instructions for particular medications. Loop diuretics are preferred, although thiazide diuretics may be helpful in managing high blood pressure. Reducing body weight in obese patients and increasing exercise can improve symptomatology and exercise capacity and should therefore be considered in appropriate patients. It is important to identify and treat the underlying risk factors, etiology and comorbidities coexisting in HFpEF (eg, hypertension, ischemic coronary heart disease, amyloidosis, atrial fibrillation). Undoubtedly, the treatment of some of the basic phenotypes of HFpEF leads to improved results [3].

PHARMACOLOGICAL TREATMENT OF HEART FAILURE WITH MILDLY REDUCED EJECTION FRACTION

As with other forms of HF, diuretics should be used to control congestion. Substantial randomized prospective studies have not been performed exclusively in patients with HFmrEF. Some data can be collected from the subgroup analysis of studies for HFpEF, none of which met their primary endpoint. Although no strong recommendations can be made regarding specific therapies at this time, the ESC 2021 guideline for the management of heart failure recommends, with evidence class IIb, to reduce the risk of hospitalization and reduce mortality, the use of angiotensin-converting enzyme inhibitors, angiotensin receptor II type 1 receptor blockers, beta-blockers, mineralocorticoid receptor antagonists and angiotensin receptor-neprilysin inhibitor.

CONCLUSIONS

Heart failure with preserved and mildly reduced ejection fraction in the elderly is a

challenge for the clinician, both in terms of diagnosis, prognosis and treatment. The clinical presentation of heart failure is often atypical and may be masked by the presence of comorbidities. Preserved ejection fraction heart failure is a common occurrence in elderly patients. The risk of morbidity and mortality for this type of heart failure is comparable to other classes of heart failure, for whom etiological treatment is the only one that brings significant benefits in terms of survival and quality of life. Heart failure with a mildly reduced ejection fraction is phenotypically similar to heart failure with a preserved ejection fraction, but etiologically and therapeutically similar to that with a reduced ejection fraction. Currently there is no clear evidence regarding the therapeutic benefits, being a subject that requires further studies. In elderly patients, a multidimensional geriatric assessment should be performed to identify comorbidities and their risks for decompensation and functional consequences, to allow for the proper adjusting of therapies.

Conflicts of interest

The authors declare no conflicts of interest.

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